Pneumococcal Conjugate Vaccine Breakthrough Infections: 2001–2016

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abstract

BACKGROUND: Most countries use 3-dose pneumococcal conjugate vaccine (PCV) schedules; a 4-dose (3 primary and 1 booster) schedule is licensed for US infants. We evaluated the invasive pneumococcal disease (IPD) breakthrough infection incidence in children receiving 2 vs 3 primary PCV doses with and without booster doses (2 + 1 vs 3 + 1; 2 + 0 vs 3 + 0).

METHODS: We used 2001–2016 Active Bacterial Core surveillance data to identify breakthrough infections (vaccine-type IPD in children receiving ≥1 7-valent pneumococcal conjugate vaccine [PCV7] or 13-valent pneumococcal conjugate vaccine [PCV13] dose) among children aged <5 years. We estimated schedule-specific IPD incidence rates (IRs) per 100 000 person-years and compared incidence by schedule (2 + 1 vs 3 + 1; 2 + 0 vs 3 + 0) using rate differences (RDs) and incidence rate ratios.

RESULTS: We identified 71 PCV7 and 49 PCV13 breakthrough infections among children receiving a schedule of interest. PCV13 breakthrough infection rates were higher in children aged <1 year receiving the 2 + 0 (IR: 7.8) vs 3 + 0 (IR: 0.6) schedule (incidence rate ratio: 12.9; 95% confidence interval: 4.1–40.4); PCV7 results were similar. Differences in PCV13 breakthrough infection rates by schedule in children aged <1 year were larger in 2010–2011 (2 + 0 IR: 18.6; 3 + 0 IR: 1.4; RD: 16.6) vs 2012–2016 (2 + 0 IR: 3.6; 3 + 0 IR: 0.2; RD: 3.4). No differences between schedules were detected in children aged ≥1 year for PCV13 breakthrough infections.

CONCLUSIONS: Fewer PCV breakthrough infections occurred in the first year of life with 3 primary doses. Differences in breakthrough infection rates by schedule decreased as vaccine serotypes decreased in circulation.

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WHAT'S KNOWN ON THIS SUBJECT: A 4-dose pneumococcal conjugate vaccine (PCV) schedule is used in the United States; most other countries use 3-dose schedules. These 3-dose schedules have effectively reduced invasive pneumococcal disease and colonization; whether a 4-dose schedule better controls disease is unknown.

WHAT THIS STUDY ADDS: Incidence of invasive pneumococcal disease breakthrough infections was lower in the first year of life for children receiving 3 vs 2 primary PCV doses. Differences between schedules are reduced as vaccine serotypes decrease in circulation.

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Seven-valent pneumococcal conjugate vaccine (PCV7) was introduced for US children in 2000 on a 4-dose schedule, with primary doses at 2, 4, and 6 months and a booster at 12 to 15 months.[1] In 2010, 13-valent pneumococcal conjugate vaccine (PCV13) replaced PCV7 on the same schedule.[2] Introduction of pneumococcal conjugate vaccines (PCVs) dramatically decreased invasive pneumococcal disease (IPD) incidence in US children aged <5 years.[3,4] Despite high vaccination coverage, not all US children receive the full number of recommended doses. In 2016, 81.8% of children 19 to 35 months of age received ≥4 PCV doses.[5]

In 2012, the World Health Organization recommended PCV use on a 3-dose schedule, either 2 primary doses with a booster or 3 primary doses without a booster,[6] after studies revealed the immunogenicity of 3-dose schedules and their effectiveness in reducing disease and colonization.[7–9] A US postlicensure case-control study revealed that PCV7 effectiveness against IPD with 3-dose and 4-dose schedules was similar.[10] Accordingly, many countries introduced PCVs on a 3-dose schedule or switched from 4-dose to 3-dose schedules.[11,12] As of September 2018, 117 of 143 countries using PCVs use a 3-dose schedule, with most developed countries using a schedule with a booster dose.[13]

Although PCV is highly effective in preventing IPD,[14] infection can occur in children who are partially or fully vaccinated.[15] Because not all US children receive the recommended 4 PCV doses, we were able to use multisite, population-based surveillance data to describe breakthrough infections among US children aged <5 years receiving ≥1 dose of PCV7 or PCV13 by schedule. Our primary objective was to evaluate whether a 3-dose schedule with 2 primary doses is associated with increased infection risk before and after the booster dose, compared with the US-recommended 4-dose schedule with 3 primary doses.

METHODS

IPD Case Identification

Cases were identified through routine Active Bacterial Core surveillance (ABCs),[16] a laboratory- and population-based surveillance system operating in 10 US sites with 33.8 million people under pneumococcal surveillance in 2017.[17] IPD cases were defined as identification of pneumococcus from a normally sterile body site (eg, blood, cerebrospinal fluid, or pleural fluid). Medical charts were reviewed for demographic information, infection type, and medical history, including chronic and immunocompromising conditions. Pneumococcal isolates were sent to the Centers for Disease Control and Prevention (CDC) or the Minnesota Public Health laboratory for serotype assignments. In 2015 and 2016, serotyping was assigned through the CDC *Streptococcus* Laboratory genomic bioinformatics pipeline.[18]

PCV7 and PCV13 Breakthrough Infections

During 2001–2016, IPD surveillance among children 2 months to 5 years of age included complete immunization histories, obtained by contacting health care providers and reviewing state immunization registries. We defined PCV7 breakthrough infection as IPD caused by a PCV7 serotype (4, 6B, 9V, 14, 18C, 19F, or 23F) in a child who received at least 1 dose of PCV7 ≥2 weeks before the date of the pneumococcal culture. PCV13 breakthrough infection was defined as IPD caused by a PCV13 serotype (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, or 23F) in a child who received at least 1 dose of PCV13 ≥2 weeks before the pneumococcal culture date. Breakthrough infections in children with mixed vaccine formulations (PCV7 and PCV13) were categorized by the vaccine of which they received the most doses. A vaccine dose was only considered valid if it was received ≥2 weeks before the culture date.

We defined primary doses as PCV doses received before 8 months of age and booster doses as PCV doses received at 12 to 16 months of age. PCV7 and PCV13 breakthrough infections were classified by PCV schedule received before the breakthrough infection as follows:

Disease after the primary series only:

1. 2 primary doses, no booster (2 + 0)
2. 3 primary doses, no booster (3 + 0)

Disease after the primary series and booster dose:

3. 2 primary doses with booster (2 + 1)
4. 3 primary doses with booster (3 + 1)

Children who received ≥1 PCV dose but did not fit into these classifications because of dose timing were grouped into an "other schedule" category and were only included in descriptive analysis.

Statistical Analysis

We performed a descriptive analysis of breakthrough infections in children with a known vaccine history, which included demographics, clinical presentation, comorbid conditions, and infecting strain serotype. We used Poisson regression to calculate vaccine schedule–specific incidence rates (IRs), along with rate differences (RDs), incidence rate ratios (IRRs), and 95% confidence intervals (CIs). For population denominators for breakthrough infection rates, we used vaccination coverage data from the National Immunization Survey–Child[19] to estimate the number of children

vaccinated on any given schedule by age. We combined 2001–2016 survey data for states in the ABCs system by vaccine type (PCV7 or PCV13), birth cohort, and length of follow-up for each schedule (Table 1). For 2 + 1 and 3 + 1 schedules, booster doses were included for the denominator population if given through the end of the follow-up period (ie, age 24 or 35 months) because of data source limitations. We calculated the number of children receiving each schedule by multiplying the number of children in each ABCs birth cohort by vaccination coverage estimates. Denominators were matched to corresponding numerators from ABCs by vaccine type, schedule, birth cohort, and follow-up period.

We estimated IRs and IRRs stratified by age at follow-up (Table 1). For breakthrough infections after receipt of 2 + 0 and 3 + 0 schedules, we calculated rates of breakthrough IPD at <12 months and at 12 to 35 months of age. For breakthrough infections after receipt of 2 + 1 and 3 + 1 schedules, we calculated breakthrough IPD rates at 12 to 23 and 24 to 59 months of age. For children receiving 2 + 0 and 3 + 0 schedules, we evaluated breakthrough infections until 35 months on the basis of available National Immunization Survey–Child vaccination coverage data. For children receiving 2 + 1 and 3 + 1 schedules, we evaluated breakthrough infections occurring through 59 months; however, when estimating the denominator, vaccine doses could only be ascertained through 35 months of age; we assumed that receipt of a booster dose by 35 months reflected children's final vaccination status. For all rate comparisons, we considered a 2-tailed $P < .05$ as statistically significant.

For rate calculations, we assumed children with IPD with unknown vaccine histories had the same distribution of PCV status as children with a known vaccine history who received 1 of 5 possible schedules (2 + 0, 3 + 0, 2 + 1, 3 + 1, or any other) or were unvaccinated. We performed multiple imputation to impute vaccination status and schedule for children with a missing history by fully conditional specification using Markov chain Monte Carlo methods.[20,21] Predictors of vaccination schedule included PCV7 versus PCV13 breakthrough infection, age at infection, birth year, case calendar year, infection serotype, state where case occurred, interaction between age at infection and case calendar year, and interaction between age at infection and birth year. Standard methods were used to combine estimates from multiply imputed data sets.[22] We conducted a sensitivity analysis excluding all children with unknown vaccine histories on the assumption that they were more likely to be unvaccinated.

To evaluate changes in rates over time due to herd immunity, we performed a subanalysis of PCV13 breakthrough infections in the first year of life for children receiving 2 + 0 and 3 + 0 schedules in early post-PCV13 (2010–2011) and late post-PCV13 (2012–2016) time periods. We estimated cases averted in a setting of a schedule with 3 primary doses, compared with 2 primary doses, using calculated breakthrough infection rates for each schedule and

TABLE 1 Numerator and Denominator Definitions for Estimating Rates of IPD Breakthrough Infections by Vaccination Schedule and Follow-up Period

Age at IPD Diagnosis	Schedules With 2 Primary Doses With and Without the Booster	Schedules With 3 Primary Doses With and Without the Booster
<12 mo	2+0 Schedule	3+0 Schedule
Numerator	No. IPD cases at age <12 mo after 2 doses of PCV before 8 mo of age	No. IPD cases at age <12 mo after 3 doses of PCV before 8 mo of age
Denominator	No. children receiving 2 doses of PCV before 8 mo of age and 0 additional doses of PCV by 12 mo of age	No. children receiving 3 doses of PCV before 8 mo and 0 additional doses of PCV by 12 mo
12–35 mo	2+0 Schedule	3+0 Schedule
Numerator	No. IPD cases at age 12–35 mo after 2 doses of PCV before 8 mo of age	No. IPD cases at age 12–35 mo after 3 doses of PCV before 8 mo of age
Denominator	No. children receiving 2 doses of PCV before 8 mo of age and 0 additional doses of PCV by 35 mo of age	No. children receiving 3 doses of PCV before 8 mo of age and 0 additional doses of PCV by 35 mo
12–23 mo	2+1 Schedule	3+1 Schedule
Numerator	No. IPD cases at age 12–23 mo after 2 doses of PCV before 8 mo of age and 1 dose of PCV at 12–16 mo	No. IPD cases at age 12–23 mo after 3 doses of PCV before 8 mo of age and 1 dose of PCV at 12–16 mo
Denominator	No. children receiving 2 doses of PCV before 8 mo of age and 1 dose of PCV at 12–24 mo[a]	No. children receiving 3 doses of PCV before 8 mo of age and 1 dose of PCV at 12–24 mo[a]
24–59 mo	2+1 Schedule	3+1 Schedule
Numerator	No. IPD cases at age 24–59 mo after 2 doses of PCV before 8 mo of age and 1 dose of PCV at 12–16 mo	No. IPD cases at age 24–59 mo after 3 doses of PCV before 8 mo of age and 1 dose of PCV at 12–16 mo
Denominator	No. children receiving 2 doses of PCV before 8 mo of age and 1 dose of PCV at 12–35 mo[a]	No. children receiving 3 doses of PCV before 8 mo of age and 1 dose of PCV at 12–35 mo[a]

Numerator data are from the ABCs system. Denominator data are from the National Immunization Survey–Child.

[a] Denominators for the 2 + 1 and 3 + 1 schedules include booster doses given through the end of the follow-up period.

live birth estimates from the CDC's National Vital Statistics System.

RESULTS

Characteristics of PCV7 and PCV13 Breakthrough Infections

ABCs identified 5997 cases of IPD from 2001 to 2016 in children aged <5 years. We included 121 PCV7 breakthrough infections and 111 PCV13 breakthrough infections with verified vaccine histories in the descriptive analysis. We excluded 5765 IPD cases from the descriptive analysis because of an unknown serotype (*n* = 834), a non-PCV7 or non-PCV13 serotype (*n* = 2243), no confirmed vaccine history (*n* = 671), unvaccinated status (*n* = 598), IPD caused by a PCV13-unique serotype in a child vaccinated with PCV7 (*n* = 1405), or birth year before 2000 (*n* = 14) (Fig 1). Demographic characteristics and comorbid conditions among children with breakthrough infections are shown in Table 2, and serotypes causing breakthrough infections are shown in Tables 3 and 4.

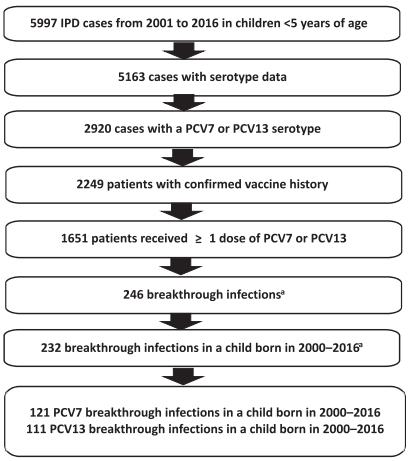

FIGURE 1
Cases included in analysis of PCV7 and PCV13 breakthrough infections, ABCs, 2001–2016. [a] A PCV7 breakthrough infection is defined as vaccine-type IPD in a child who received ≥1 PCV7 dose. A PCV13 breakthrough infection is defined as vaccine-type IPD in a child who received ≥1 PCV13 dose.

PCV7 Breakthrough Infections

Most PCV7 breakthrough infections occurred in the 5 years after vaccine introduction (Fig 2). The most common clinical syndrome among children with breakthrough infections was bacteremia without a focus (54.5%), which was also the most common clinical syndrome among overall IPD cases during the PCV7 era (2001–2009). Among the 4 schedules of interest, breakthrough infections occurred most often after a 3 + 0 schedule (32 of 71 [45%]; Table 3). For 2 + 0 and 3 + 0 schedules, there were 10 of 15 (67%) and 2 of 32 (6%) breakthrough infections in the first year of life, respectively, with the following breakdown of infections by age: 0 to 5 months: 0 of 10 and 0 of 2; 6 to 7 months: 4 of 10 and 0 of 2; and 8 to 11 months: 6 of 10 and 2 of 2.

Among other schedules, those most frequently associated with breakthrough infections included 1- (*n* = 31), 2- (*n* = 4), 3- (*n* = 8), and 4-dose (*n* = 7) PCV7 schedules (50 of 121 [41%]). Children who only received 1 PCV7 dose as an infant (*n* = 31) or toddler (*n* = 0) accounted for 26% of breakthrough infections, and among children receiving 1 infant dose, most breakthrough infections occurred in the first year of life (24 of 31). Most PCV7 breakthrough infections were due to serotypes 19F (51.2%) and 6B (17.4%) (Table 3).

PCV13 Breakthrough Infections

The period of observation for PCV13 breakthrough infections was limited to 6 years post introduction (Fig 2). The most common syndrome in PCV13 breakthrough infections was bacteremic pneumonia (63.1%); bacteremia without a focus remained the most common clinical syndrome among overall IPD cases during the same time period (2010–2016). In contrast to PCV7 breakthrough infections, PCV13 breakthrough infections occurred most often after a 3 + 1 schedule (30 of 49 [61%]; Table 4). For 2 + 0 and 3 + 0 schedules, there were 7 of 9 (78%) and 5 of 9 (56%) breakthrough infections in the first year of life, respectively, with the following breakdown of infections by age: 0 to 5 months: 1 of 7 and 0 of 5; 6 to 7 months: 5 of 7 and 2 of 5; and 8 to 11 months: 1 of 7 and 3 of 5.

For other schedules, those most frequently associated with breakthrough infections included 1- (*n* = 35), 2- (*n* = 10), 3- (*n* = 7), and 4-dose (*n* = 10) PCV13 schedules (62 of 111 [56%]; Table 4). Children who only received 1 PCV13 dose as an infant (*n* = 26) or toddler (*n* = 9) accounted for 31% of breakthrough infections, and similar to PCV7 breakthrough infections, most PCV13 breakthrough infections occurred during the first year of life for children receiving 1 infant dose (22 of 26). PCV13 breakthrough infections were primarily due to serotypes 19A (59.5%) and 3 (29.7%).

Rates of Breakthrough Infections in Schedules With 2- vs 3-Dose Primary Series

Disease rates were estimated by using 232 breakthrough infections with confirmed vaccination histories and 160 cases for which multiple imputation was performed because of an unknown vaccine history and disease caused by either a PCV7 serotype (for IPD cases from 2001 to February 2010) or disease caused by a PCV13 serotype (for IPD cases after February 28, 2010) (Table 5).

PCV7 Breakthrough Infection Rates

Rates of disease were highest in the first year of life among children receiving 2 primary doses (IR: 7.0 cases per 100 000 person-years). Breakthrough infection rates in the first year of life were significantly higher among children who received 2 vs 3 doses (IRR: 21.8; 95% CI: 5.3–89.3), although rates were not significantly different between the 2 schedules at 12 to 35 months of age (Table 5). Among children receiving

TABLE 2 Characteristics of Children <5 Years of Age With IPD, ABCs, 2001–2016

	PCV7 Breakthrough Cases, *n* (%)[a]	PCV7-Type IPD 2001–2009, *n* (%)	All IPDs 2001–2009, *n* (%)	PCV13 Breakthrough Cases, *n* (%)[a]	PCV13-Type IPD 2010–2016, *n* (%)	All IPDs 2010–2016, *n* (%)
	N = 121	*N* = 745	*N* = 4359	*N* = 111	*N* = 475	*N* = 1653
ABCs site						
California	13 (10.7)	61 (8.2)	313 (7.1)	9 (8.1)	36 (7.6)	114 (6.9)
Colorado	10 (8.3)	70 (9.4)	313 (7.1)	9 (8.1)	44 (9.3)	118 (7.1)
Connecticut	7 (5.8)	78 (10.5)	369 (8.5)	7 (6.3)	35 (7.4)	107 (6.5)
Georgia	23 (19.0)	150 (20.1)	934 (21.4)	25 (22.5)	73 (15.4)	296 (18.0)
Maryland	8 (6.6)	82 (11.0)	387 (8.9)	11 (9.9)	40 (8.4)	129 (7.8)
Minnesota	19 (15.7)	100 (13.4)	744 (17.1)	16 (14.4)	90 (19.0)	322 (19.5)
New Mexico	2 (1.7)	3 (0.4)	219 (5.0)	11 (9.9)	35 (7.4)	126 (7.6)
New York	16 (13.2)	62 (8.3)	286 (6.6)	12 (10.8)	52 (11.0)	143 (8.7)
Oregon	9 (7.4)	38 (5.1)	157 (3.6)	5 (4.5)	18 (3.8)	51 (3.1)
Tennessee	14 (11.6)	101 (13.6)	637 (14.6)	6 (5.4)	52 (11.0)	247 (14.9)
Age, mo						
<12	38 (31.4)	196 (26.3)	1453 (33.3)	34 (30.6)	155 (32.6)	546 (33.0)
0–5	17 (14.0)	104 (14.0)	636 (14.6)	13 (11.7)	89 (18.7)	268 (16.2)
6–11	21 (17.4)	92 (12.3)	817 (18.7)	21 (18.9)	66 (13.9)	278 (16.8)
12–23	36 (29.8)	198 (26.6)	1353 (31.0)	25 (22.5)	105 (22.1)	454 (27.5)
24–35	22 (18.2)	143 (19.2)	691 (15.9)	15 (13.5)	89 (18.7)	271 (16.4)
36–47	14 (11.6)	129 (17.3)	493 (11.3)	23 (20.7)	72 (15.2)	189 (11.4)
48–59	11 (9.1)	79 (10.6)	369 (8.5)	14 (12.6)	54 (11.4)	193 (11.7)
Male sex	76 (62.8)	444 (59.6)	2523 (57.9)	64 (57.7)	265 (56.8)	934 (56.5)
Race						
White	91 (75.2)	412 (55.3)	2447 (56.1)	59 (53.2)	265 (55.8)	892 (54.0)
African American	18 (14.9)	234 (31.4)	1291 (29.6)	34 (30.6)	133 (28.0)	483 (29.2)
American Indian or Alaskan native	0 (0.0)	3 (0.4)	123 (2.8)	9 (8.2)	21 (4.4)	59 (3.6)
Asian American or Pacific Islander	3 (2.5)	25 (3.4)	188 (4.3)	5 (4.5)	20 (4.2)	98 (5.9)
Other	3 (2.5)	17 (2.3)	59 (1.4)	1 (0.9)	2 (0.4)	7 (0.4)
Unknown	6 (5.0)	54 (7.3)	251 (5.8)	3 (2.7)	34 (7.2)	114 (6.9)
Ethnicity						
Hispanic or Latino	25 (20.7)	111 (14.9)	626 (14.4)	18 (16.2)	78 (16.4)	233 (14.1)
Not Hispanic or Latino	83 (49.1)	463 (62.2)	3087 (70.8)	86 (77.5)	360 (75.8)	1287 (77.9)
Unknown	13 (10.7)	171 (23.0)	646 (14.8)	7 (6.3)	37 (7.8)	133 (8.1)
Clinical syndrome[b]						
Bacteremia without a focus	66 (54.5)	385 (51.7)	2116 (48.5)	25 (22.5)	150 (31.6)	729 (44.1)
Bacteremic pneumonia	24 (19.8)	218 (29.3)	1413 (32.4)	70 (63.1)	232 (48.8)	512 (31.0)
Empyema	2 (1.7)	1 (0.13)	89 (2.0)	19 (17.1)	45 (9.6)	59 (3.6)
Meningitis	17 (14.1)	72 (9.7)	335 (7.7)	5 (4.9)	34 (7.2)	173 (10.5)
Osteomyelitis or septic arthritis	2 (1.7)	7 (0.9)	86 (2.0)	3 (2.7)	13 (2.7)	51 (3.1)
Chronic medical condition[b,c]	9 (7.4)	52 (7.0)	315 (7.2)	8 (7.2)	27 (5.7)	112 (6.8)
Immunosuppressive medical condition[b,d]	18 (14.9)	42 (5.6)	195 (4.5)	6 (5.4)	25 (5.3)	159 (9.6)
Hospitalized	59 (49.2)	349 (47.0)	2267 (52.4)	95 (86.4)	373 (78.7)	1155 (70.2)
Died	3 (2.5)	19 (2.6)	71 (1.6)	3 (2.7)	6 (1.3)	35 (2.1)

[a] Breakthrough infections included have verified vaccination histories.

[b] Subcategories were not mutually exclusive (with the exception of bacteremia without a focus).

[c] Chronic diseases include asthma, atherosclerotic cardiovascular disease, diabetes, chronic obstructive pulmonary disease, heart failure, cerebrospinal fluid leak, cochlear implant, cerebrovascular unintentional injury.

[d] Immunosuppressive medical conditions include immunoglobulin deficiency, immunosuppressive therapy, leukemia, nephrotic syndrome, sickle cell, asplenia, Hodgkin's lymphoma, bone marrow transplant, complement deficiency.

schedules with a booster dose, those receiving a 2 + 1 schedule had a significantly higher rate of breakthrough infection in the second year of life (IRR: 9.2; 95% CI: 2.2–37.4), which declined but remained significant with longer follow-up (IRR: 3.6; 95% CI: 1.2–11.1), compared with a 3 + 1 schedule.

PCV13 Breakthrough Infection Rates

Rates of disease were also highest in the first year of life among children receiving 2 primary doses (IR: 7.8 cases per 100 000 person-years). Similar to PCV7 breakthrough infections, the rate of disease was significantly higher in the first year of life for children who received 2 vs 3 doses (IRR: 12.9; 95% CI: 4.1–40.4),

TABLE 3 PCV7 Breakthrough Infections Among Children Aged <5 Years With Verified Vaccination Histories by Vaccine Schedule, ABCs, 2001–2016

Serotype	No. Cases by PCV7 Schedule					Total, *N* (%)
	2 + 0	3 + 0	2 + 1	3 + 1	Other[a]	
Total PCV7 cases	15 (12.4%)	32 (26.4%)	7 (5.8%)	17 (14.0%)	50 (41.3%)	121
4	0	7	0	1	3	11 (9.1)
6B	5	1	0	2	13	21 (17.4)
9V	0	0	0	0	2	2 (1.7)
14	1	1	0	0	5	7 (5.8)
18C	2	3	2	1	4	12 (9.9)
19F	6	18	5	13[b]	20	62 (51.2)
23F	1	2	0	0	3	6 (5.0)

[a] The "other" category includes other 1-, 2-, 3-, and 4-dose PCV7 schedules.
[b] Includes 1 mixed vaccine-type schedule (received 3 doses of PCV7 and 1 dose of PCV13).

but no significant differences were found between the schedules with longer follow-ups. In contrast to PCV7 breakthrough infections, no significant differences in rates of disease were observed between children receiving 2 + 1 vs 3 + 1 schedules during any follow-up period.

Sensitivity Analysis

In the sensitivity analysis, excluding children without verified vaccination histories, rates of breakthrough IPD were lower; however, differences in breakthrough infection rates between schedules before and after PCV7 and PCV13 booster doses remained similar to those in the primary analysis (Table 6).

PCV13 Breakthrough Infections by Time Since Vaccine Introduction

We compared rates of PCV13 breakthrough infections in the first year of life after receipt of 2 vs 3 primary doses, stratified by early (2010–2011) and late (2012–2016) post-PCV13 periods (Fig 3). In the early post-PCV13 period (2010–2011), the 2 + 0 schedule was associated with 16.6 additional cases per 100 000 person-years compared with the 3 + 0 schedule. During the later post-PCV13 period (2012–2016), the difference between the 2 schedules declined (2 + 0 IR: 3.6; 3 + 0 IR: 0.2; RD: 3.4 cases per 100 000 person-years). We estimated that in the first year of life, a schedule with 3 primary doses prevented 330 PCV13 breakthrough infections in the United States annually, compared with a schedule with 2 primary doses in the early years after vaccine introduction (2010–2011). However, in the late post-PCV13 period (2012–2016), the number of cases prevented annually in the first year of life by using 3 vs 2 primary doses decreased to 55.

DISCUSSION

In the PCV era in the United States, vaccine breakthrough infections occur, but incidence is low among children <5 years old. Our findings are similar to those reported in the United States shortly after PCV7 introduction and in other countries after PCV7 and PCV13 introduction.[15,23] In the first year of life before the booster dose is given, a schedule with 3 primary doses resulted in significantly fewer breakthrough infections than a schedule with 2 primary doses. After the first year of life, differences were no longer observed between schedules with 3 vs 2 primary doses for PCV13 breakthrough infections, with or without booster doses; however, for PCV7, a schedule with 3 primary doses was associated with fewer breakthrough infections compared with a schedule with 2 doses, even after a booster dose.

PCV7 immunogenicity studies have shown that 3 primary doses induce higher antibody levels (geometric mean concentrations [GMCs]) than 2 primary doses before, but not after, booster dose for some serotypes, particularly 6B and 23F.[7,24,25] In the United States, differences seen in

TABLE 4 PCV13 Breakthrough Infections Among Children Aged <5 Years With Verified Vaccination Histories by Vaccine by Schedule, ABCs, 2010–2016

Serotype	No. Cases by PCV13 Schedule					Total, *N* (%)
	2 + 0	3 + 0	2 + 1	3 + 1	Other[a]	
Total PCV13 cases	9 (8.1%)	9 (8.1%)	1 (0.9%)	30 (27.0%)	62 (55.9%)	111
3	1	2	1	10	19	33 (29.7)
7F	0	0	0	1	1	2 (1.8)
14	0	0	0	0	1	1 (0.9)
19A	7	5	0	16	38	66 (59.5)
19F	1	2	0	3	2	8 (7.2)
23F	0	0	0	0	1	1 (0.9)

[a] The "other" category includes other 1-, 2-, 3-, and 4-dose PCV13 schedules.

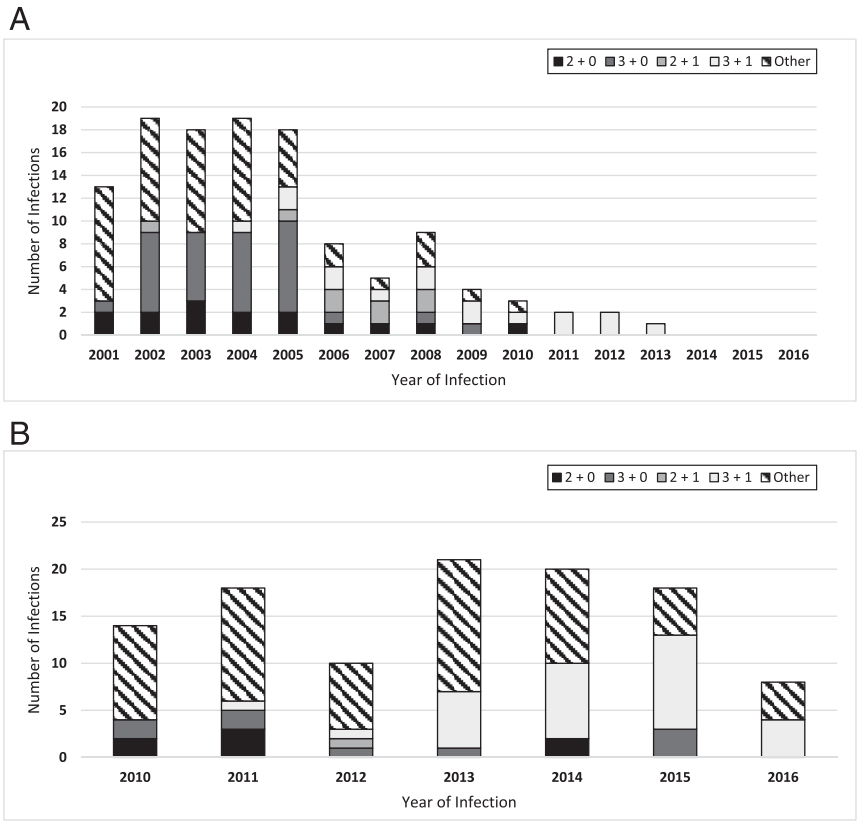

FIGURE 2

A, PCV7 breakthrough infections among children aged <5 years with verified vaccination histories by calendar year and vaccine schedule, ABCs, 2001–2016. B, PCV13 breakthrough infections among children aged <5 years with verified vaccination histories by calendar year and vaccine schedule, ABCs, 2010–2016.

immune response for serotypes 6B and 23F may no longer be relevant because these PCV7 serotypes now rarely circulate or cause disease.[26] PCV13 immunogenicity studies with head-to-head comparisons of dosing schedules revealed that a 2-dose primary schedule elicits lower antibody GMCs than a 3-dose primary schedule for most serotypes; however, there was little difference in the proportion of subjects with antibody concentrations above the accepted threshold of 0.35 μg/mL (percent responders).[27,28] Serotypes 19A and 3 contributed to most PCV13 breakthrough infections in our study; serotype 3 immunogenicity studies revealed similar GMCs and percent responders after either 3-dose or 2-dose primary series, whereas serotype 19A GMCs favored a 3-dose schedule. Clinical relevance of these differences in immune response is unclear because the 0.35-μg/mL threshold was developed for PCV licensure on the basis of overall efficacy against all serotypes and is not serotype specific.[29] Andrews et al[30] showed that correlates of protection may vary by serotype, and the estimated threshold of protection against IPD caused by serotypes 3, 19A, and 19F was much higher (2.83, 1.00, and 1.17 μg/mL, respectively) compared with the estimated threshold of protection against IPD caused other PCV13 serotypes (0.14–0.87 μg/mL).

Although our analysis was only focused on IPD, the effect of PCV schedules on vaccine-type nasopharyngeal colonization is also important because reductions in colonization and subsequent indirect (herd) protection may be critical to the overall success of PCV programs. PCV7 colonization studies revealed findings similar to ours for 3 primary doses in the first year of life before the booster dose. Schedules with 3 primary doses had lower vaccine-type carriage rates than schedules with 2 primary doses 1 to 7 months before the booster dose; however, no differences were noted at age 12 months, before or after the booster dose.[9,31–33] Differences between schedules were less apparent in PCV13 colonization studies.[34–37] Because colonization does not always lead to disease, implications of differences in colonization effects by schedule may be difficult to extrapolate to direct effects on disease; the effect of different schedules on clinical outcomes should be considered together with immunogenicity and colonization studies. With our study, we provide an understanding of differences in rates of IPD observed among children vaccinated in real-life settings using different PCV schedules within a single population.

Because the United States has a mature immunization program with high vaccination coverage and low disease rates and informed by the successful implementation of PCV programs with 2 + 1 schedules in other developed countries,[5,26] the Advisory Committee on Immunization Practices has discussed changes to the routine PCV13 schedule. Our analysis provides additional data for consideration. Although we observed higher rate of disease in the first year of life with 2 vs 3 primary doses, differences in breakthrough infections by schedule decreased as vaccine uptake in the population increased and vaccine serotypes decreased in circulation. Our analysis supports a decline over time after PCV introduction in breakthrough infections, a reduction in absolute RDs when comparing the 2 schedules, and in breakthrough

TABLE 5 IR (Cases per 100 000 Person-Years) of PCV7 and PCV13 Breakthrough Infections Among Children Aged <5 Years With Verified and Imputed Vaccination Histories by Age at Time of Disease and Vaccine Schedule, ABCs, 2001–2016

	PCV7 Breakthrough Cases					PCV13 Breakthrough Cases				
	IR		RD	IRR (95% CI)	*P*	IR		RD	IRR (95% CI)	*P*
	Schedules with 2 Primary Doses With and Without the Booster	Schedules with 3 Primary Doses With and Without the Booster				Schedules with 2 Primary Doses With and Without the Booster	Schedules with 3 Primary Doses With and Without the Booster			
Schedule	2 + 0	3 + 0				2 + 0	3 + 0			
Age at Disease										
<12 mo	7.00	0.32	6.68	21.75 (5.30–89.26)	<.01	7.79	0.60	7.19	12.89 (4.11–40.44)	<.01
12–35 mo	4.53	5.27	−0.74	0.86 (0.34–2.20)	.75	1.31	2.34	−1.03	0.56 (0.06–4.93)	.60
Median age, mo	10	22	—	—	—	7	11	—	—	—
Schedule	2 + 1	3 + 1				2 + 1	3 + 1			
Age at Disease										
12–23 mo	2.92	0.32	2.6	9.15 (2.24–37.44)	<.01	0.12	0.57	−0.45	0.22 (0.00–111.64)	.68
≥24 mo	1.04	0.29	0.75	3.63 (1.19–11.07)	.02	0.68	0.47	0.21	1.45 (0.18–11.71)	.72
Median age, mo	27	36	—	—	—	24	34	—	—	—

—, not applicable.

infections averted by using a schedule with 3 vs 2 primary doses. Differences in breakthrough IPD incidence after the booster dose were observed for children receiving 2 vs 3 primary doses of PCV7 but not PCV13. This could be due to differences in serotypes (PCV7- versus PCV13-unique types), PCV7 vaccine shortages that resulted in temporary removal of the booster dose for healthy children, or a more robust catch-up campaign with introduction of PCV13.

Colonization studies performed in the United States in 2010–2013 revealed that PCV7 serotypes are no longer carried and that PCV13 serotype carriage is low, suggesting low overall likelihood of exposure to vaccine serotypes and, consequently, risk of disease caused by these serotypes.[38] Our analysis supports this because 90% of PCV13 breakthrough infections were due to 2 serotypes, 19A and 3, and PCV7 serotypes rarely caused disease. These results are not surprising because serotype 19A was the most common serotype among children before PCV13 introduction.[39–41] Postlicensure studies in which PCV13 effects on serotype 3 were evaluated revealed mixed results regardless of the schedule,[14,30] with most revealing limited or no effectiveness.[29,42–44]

On a population level, declines in IPD have been observed in countries using 3-dose schedules as early as 1 to 2 years after vaccine introduction.[8,45,46] Despite successes in settings using 3-dose schedules, there would be practical considerations for the vaccine policy-makers before adopting a 2 + 1 schedule. For example, it should be determined whether this change could lead to increased disparities in coverage and disease among groups at increased risk.

Our study has limitations. Our estimation of cases averted is based on the assumption that vaccination

TABLE 6 Sensitivity Analysis of the IR (Cases per 100 000 Person-Years) of PCV7 and PCV13 Breakthrough Infections Among Children Aged <5 Years With Verified Vaccination Histories by Age at Time of Disease and Vaccine Schedule, 2001–2016

Age at Disease	PCV7 Breakthrough Cases					PCV13 Breakthrough Cases				
	IR		RD	IRR (95% CI)	*P*	IR		RD	IRR (95% CI)	*P*
	Schedules with 2 Primary Doses With and Without the Booster	Schedules with 3 Primary Doses With and Without the Booster				Schedules with 2 Primary Doses With and Without the Booster	Schedules with 3 Primary Doses With and Without the Booster			
Schedule	2 + 0	3 + 0				2 + 0	3 + 0			
Age at Disease										
<12 mo	4.37	0.19	4.18	23.15 (5.07–105.68)	<.01	7.30	0.57	6.73	12.76 (4.05–40.20)	<.01
12–35 mo	2.35	4.13	−1.78	0.57 (0.20–1.64)	.30	1.27	1.92	−0.65	0.66 (0.07–5.89)	.71
Median age (mo)	10	21	—	—	—	7	11	—	—	—
Schedule	2 + 1	3 + 1				2 + 1	3 + 1			
Age at Disease										
12–23 mo	1.91	0.24	1.67	7.97 (1.78–35.63)	.01	0.0	0.56	−0.56	0.00	—
≥24 mo	1.03	0.24	0.79	3.17 (1.03–9.71)	.04	0.41	0.43	−0.02	0.96 (0.13–7.12)	.97
Median age (mo)	27	39	—	—	—	24	33	—	—	—

—, not applicable.

coverage was 100%, and we did not consider communities that might have had lower vaccination coverage with higher transmission rates and different disease dynamics. Among vaccine-eligible children born in 2000–2016, verified vaccination histories were not available for all children with PCV7- or PCV13-type IPD; however, we accounted for these missing data using multiple imputation, and results of comparisons of disease rates between schedules were similar in our sensitivity analysis. Rates of breakthrough infections after 2 + 1 and 3 + 1 schedules were likely underestimated because booster doses were included for the denominator population if given through the end of the follow-up period (ie, not restricted to a 12- to 16-month window). However, this did not influence rate ratios when comparing the 2 schedules because misclassification was likely nondifferential, and a small proportion of children in the United States received a booster dose after 16 months of age.[19] In our classification of PCV schedules, we did not take into account intervals between doses, and intervals between primary doses shorter than those recommended by the Advisory Committee on Immunization Practices could have reduced schedule effectiveness.[47] Lastly, because breakthrough infections are rare and most occurred after receipt of "other" vaccine schedules, we had limited statistical power to account for the impact of indirect effects and declines in circulating vaccine serotypes over time.

CONCLUSIONS

Our study revealed that breakthrough infections are rare and that a PCV13 schedule with 3 primary doses resulted in fewer breakthrough infections compared with a schedule with 2 primary doses in the first year of life before the booster dose. These

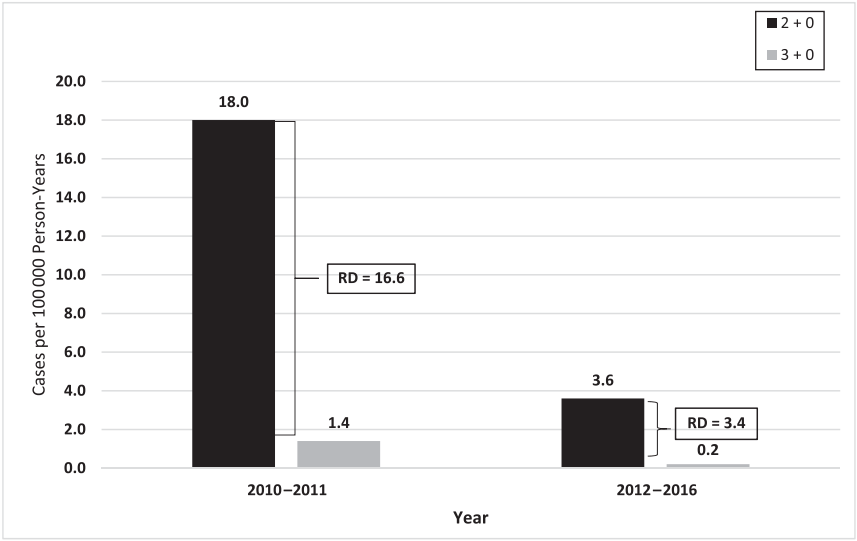

FIGURE 3

IR (cases per 100 000 person-years) of PCV13 breakthrough infections in the first year of life among children receiving a 2 + 0 vs 3 + 0 schedule based on verified and imputed vaccination histories. Rates for 2010–2011 based on verified vaccination histories only (ie, without imputing vaccine history) are the same as imputed rates. Rates for 2012–2016 by using verified vaccination histories only (ie, without imputing vaccine history) are as follows: 2 + 0 = 2.9; 3 + 0 = 0.2; RD = 2.7.

differences disappeared after the first year of life, with or without booster doses. Differences in breakthrough infection rates by schedule may be diminished in a mature immunization program context as vaccine serotypes decrease in circulation.

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ABBREVIATIONS

ABCs: Active Bacterial Core surveillance
CDC: Centers for Disease Control and Prevention
CI: confidence interval
GMC: geometric mean concentration
IR: incidence rate
IRR: incidence rate ratio
IPD: invasive pneumococcal disease
PCV: pneumococcal conjugate vaccine
PCV7: 7-valent pneumococcal conjugate vaccine
PCV13: 13-valent pneumococcal conjugate vaccine
RD: rate difference

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